

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 July 2000 (27.07.2000)

PCT

(10) International Publication Number
WO 00/43034 A3

(51) International Patent Classification⁷: **A61K 38/28**, (47/10, 47/02, 47/26)

(21) International Application Number: **PCT/US00/01627**

(22) International Filing Date: **26 January 2000 (26.01.2000)**

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:
60/117,291 26 January 1999 (26.01.1999) US

(71) Applicant (for all designated States except US): **ELI LILLY AND COMPANY [US/US]**; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **NG, Kingman [CN/US]; 10745 Putnam Place, Carmel, IN 46032 (US).**
Li, Shun [US/US]; 7620 Bancaster Drive, Indianapolis, IN 46268 (US). **WATTS, Eric, Alan [US/US]; 294 Sunrise Circle, Greenwood, IN 46142 (US).**

(74) Agents: **BENT, Stephen, A. et al.; Foley & Lardner, Suite 500, 3000 K Street, N.W., Washington, DC 20007-5109 (US).**

(81) Designated States (national): **AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.**

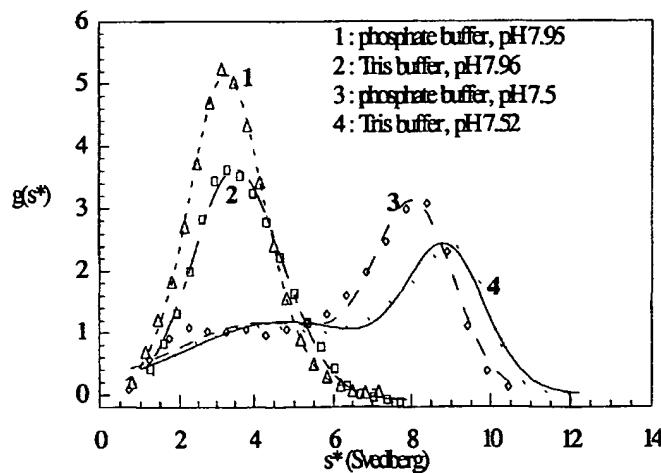
(84) Designated States (regional): **ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).**

Published:

— *With international search report.*

[Continued on next page]

(54) Title: MONODISPERSE HEXAMERIC ACYLATED INSULIN ANALOG FORMULATIONS



WO 00/43034 A3

(57) Abstract: The present invention provides formulations and methods for preparing formulations containing an aqueous solution at a pH of greater than about 7.9. The aqueous solution includes an isotonicity agent, a phenolic derivative, zinc ions, and an acylated human insulin analog. More particularly, the invention relates to formulations having a pH of greater than about 7.9 that include a monoacylated human insulin analog such as an acylated des(B30) human insulin analog or an analog that comprises a native or modified human insulin A chain optionally modified at position A21, and a modified native human insulin B chain optionally modified at position B3 and modified at position B28, or at both positions B28 and B29, and that contains a lysine residue at either position B28 or B29 acylated with a fatty acid residue. The invention also provides a method for treating a patient suffering from hyperglycemia using the pharmaceutical formulations of the invention.



— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(88) Date of publication of the international search report:
28 December 2000

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 00/01627

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/28 A61K47/10 A61K47/02 A61K47/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 48414 A (NOVO NORDISK) 24 December 1997 (1997-12-24) claims 1-18 page 5, line 5 - line 13 page 6, line 1 - line 3 ---	1-59
P, X	WO 99 34821 A (NOVO NORDISK) 15 July 1999 (1999-07-15) claims 1-14 page 9; example 1 ---	1-59
A	WO 98 34953 A (NOVO NORDISK) 13 August 1998 (1998-08-13) the whole document -----	1-59



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

7 November 2000

Date of mailing of the international search report

14/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentstaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Ventura Amat, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal ref Application No

PCT/US 00/01627

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9748414	A 24-12-1997	AU 720484	B	01-06-2000
		AU 3253697	A	07-01-1998
		BR 9709845	A	10-08-1999
		CA 2258097	A	24-12-1997
		CZ 9803956	A	12-05-1999
		EP 0921812	A	16-06-1999
		HU 9904031	A	28-04-2000
		NO 985981	A	18-12-1998
		PL 330763	A	24-05-1999
		US 5866538	A	02-02-1999
-----	-----	-----	-----	-----
WO 9934821	A 15-07-1999	AU 1870099	A	26-07-1999
		EP 1044016	A	18-10-2000
-----	-----	-----	-----	-----
WO 9834953	A 13-08-1998	AU 5749198	A	26-08-1998
		EP 0966482	A	29-12-1999
-----	-----	-----	-----	-----